Safety of live vaccines on immunosuppressive or immunomodulatory therapy—a retrospective study in three Swiss Travel Clinics

Huber, Fabienne ; Ehrensperger, Benoît ; Hatz, Christoph ; Chappuis, François ; Bühler, Silja ; Eperon, Gilles

Abstract: Background Patients increasingly benefit from immunosuppressive/immunomodulatory medications for a range of conditions allowing them a lifestyle similar to healthy individuals, including travel. However, the administration of live vaccines to immunodeficient patients bears the risk of replication of the attenuated vaccine microorganism. Therefore, live vaccines are generally contraindicated on immunosuppression. Data on live vaccinations on immunosuppressive/immunomodulatory medication are scarce. We identified all travellers seeking pre-travel advice in three Swiss travel clinics with a live vaccine during immunosuppressive/immunomodulatory therapy to ascertain experienced side effects. A retrospective and multi-centre study design was chosen to increase the sample size. Methods This study was conducted in the travel clinics of the University of Zurich; the Swiss TPH, Basel; and Geneva University Hospitals. Travellers on immunosuppressive/immunomodulatory therapy who received live vaccines [yellow fever vaccination (YFV), measles/mumps/rubella (MMR), varicella and/ or oral typhoid vaccination (OTV)] between 2008 and 2015 were identified and interviewed. A total of 60 age- and sex-matched controls (matched to Basel/Zurich travel clinics travellers) were included. Results Overall, 197 patients were identified. And 116 patients (59%) and 60 controls were interviewed. YFV was administered 92 times, MMR 21 times, varicella 4 times and OTV 6 times to patients on immunosuppressive/immunomodulatory therapy. Most common medications were corticosteroids (n = 45), mesalazine (n = 28) and methotrexate (n = 19). Live vaccines were also administered on biological treatment, e.g. TNF-alpha inhibitors (n = 8). Systemic reactions were observed in 12.2% of the immunosuppressed vs 13.3% of controls; local reactions in 7.8% of the immunosuppressed vs 11.7% of controls. In controls, all reactions were mild/moderate. In the immunosuppressed, 2/21 severe reactions occurred: severe local pain on interferon-beta and severe muscle/joint pain on sulfasalazine. Conclusion Safety of live vaccines given to immunosuppressed patients cannot be concluded. However, it is re-assuring that in the examined patient groups no serious side effects or infections by the attenuated vaccine strain occurred.

DOI: https://doi.org/10.1093/jtm/tax082

DOI: https://doi.org/10.1093/jtm/tax082

Safety of live vaccines on immunosuppressive or immunomodulatory therapy – a retrospective study in three Swiss Travel Clinics

Running Title: **Safety of live vaccines in the immunosuppressed**

Fabienne Huber [a,£]

Benoît Ehrensperger [b,£]

Christoph Hatz, MD [a,c]

François Chappuis, MD PhD [b]

Silja Bühler, MD MSc [a,$,*]

Gilles Eperon, MD [b,$]

a University of Zurich, Epidemiology, Biostatistics and Prevention Institute, Department of Public Health, Division of Infectious Diseases / Travel Clinic, Hirschengraben 84, 8001 Zurich, Switzerland. Phone: +41 44 634 4631, Fax: +41 44 634 49 84

b Geneva University Hospitals, Division of Tropical and Humanitarian Medicine, Rue Gabrielle-Perret-Gentil 6, 1205 Geneva, Switzerland. Phone: +41 22 372 96 11, Fax: +41 22 372 96 26

c Swiss Tropical and Public Health Institute, Department of Medicine and Diagnostics, Socinstrasse 57, 4051 Basel, Switzerland. Phone: +41 61 284 81 11, Fax: +41 61 284 81 01

* Corresponding author

£ Shared first co-authorship

$ Shared last co-authorship

Email addresses: fabiennehuber@bluewin.ch, Benoit.Ehrensperger@hcuge.ch, christoph.hatz@unibas.ch, francois.chappuis@hcuge.ch, silja.buehler@uzh.ch, Gilles.Eperon@hcuge.ch

Abstract

Background

Patients increasingly benefit from immunosuppressive/immunomodulatory medications for a range of conditions allowing them a lifestyle similar to healthy individuals, including travel. However, the administration of live vaccines to immunodeficient patients bears the risk of replication of the attenuated vaccine microorganism. Therefore, live vaccines are generally contraindicated on immunosuppression. Data on live vaccinations on immunosuppressive/immunomodulatory medication are scarce. We identified all travellers seeking pre-travel advice in three Swiss travel clinics with a live vaccine during immunosuppressive/immunomodulatory therapy to ascertain experienced side effects. A retrospective and multicentre study design was chosen to increase the sample size.

Methods

This study was conducted in the travel clinics of the University of Zurich, the Swiss TPH, Basel, and Geneva University Hospitals. Travellers on immunosuppressive/immunomodulatory therapy who received live vaccines (yellow fever vaccination (YFV), measles/mumps/rubella (MMR), varicella and/ or oral typhoid vaccination (OTV)) between 2008 and 2015 were identified and interviewed. Sixty age-and sex-matched controls (matched to Basel/Zurich travel clinics travellers) were included.

Results

197 patients were identified. 116 patients (59%) and 60 controls were interviewed. YFV was administered 92 times, MMR 21 times, varicella four times and OTV six times to patients on immunosuppressive/immunomodulatory therapy. Most common medications were corticosteroids (n=45), mesalazine (n=28) and methotrexate (n=19). Live vaccines were also administered on biological treatment, e.g. TNF-alpha inhibitors (n=8). Systemic reactions were observed in 12.2% of the immunosuppressed *vs.* 13.3% of controls; local reactions in 7.8% of the immunosuppressed *vs.* 11.7% of controls. In controls, all reactions were mild/moderate. In the immunosuppressed, 2/21 severe reactions occurred: severe local pain on interferon-beta and severe muscle/joint pain on sulfasalazine.

Conclusion

Safety of live vaccines given to immunosuppressed patients cannot be concluded. However, it is re-assuring that in the examined patient groups no serious side effects or infections by the attenuated vaccine strain occurred.

Key words

Live vaccine, immunosuppressive therapy; yellow fever vaccine; measles, mumps, rubella vaccine; varicella vaccine; oral typhoid vaccine

Introduction

The use of immunosuppressive/immunomodulatory medications for a wide range of underlying conditions has been rising over the past years. Patients increasingly benefit from these therapies allowing them a lifestyle similar to healthy individuals, including travel to overseas destinations [1,2]. Travel destinations do not differ between patients on immunosuppressive therapy and other travellers, including trips to high-risk areas [2–4].

Due to their immunosuppression, these patients are at higher risk to infectious diseases in term of infections, morbidity and mortality [5–9]. Consequently, immunisation is particularly important for this population.

However, the administration of live vaccines, such as yellow fever vaccination (YFV), to immunodeficient patients bears the risk of replication of the attenuated vaccine microorganism and clinically manifest infection [10–12]. Therefore, most international guidelines state that live vaccines are contraindicated in patients on immunosuppression, leading to challenging conditions in every day consultations of this vulnerable group of patients [13–15]. Some national recommendations, such as the Finnish ones, allow live vaccinations on non-biological immunosuppression after careful risk/benefit assessment [16]. In Switzerland, the vaccination recommendations allow live vaccinations on low-dose methotrexate (MTX) [17–20]. All recommendations are mostly based on expert opinion, as data are scarce. These last few years, efforts were made to evaluate the safety of some live vaccines in selected and immunosuppressed individuals. In general, primary live vaccinations are potentially more dangerous than secondary vaccinations as the immune system cannot build upon an existing immune memory to deal with the attenuated vaccine strain. In contrast, a secondary live vaccine is believed to be safer as an immune memory response can be activated and avert a systemic infection.

Measles, mumps, rubella vaccination

Several studies on secondary measles, mumps, rubella (MMR) vaccinations have been published in patients with juvenile rheumatic diseases. Patients were on treatment with classical disease modifying antirheumatic drugs (DMARDs), such as MTX and/or biological therapy with tumour necrosis factor alpha (TNFα) blocking agents or interleukin 1 (IL1) receptor antagonists and vaccination was safe [21–23]. In a prospective study, 2/28 juvenile patients received a first-time MMR vaccination [24]. In one of them (therapy with MTX and corticosteroids) fever and a skin rash appeared 20 days post-vaccination. It was concluded that the rash was part of the disease activity rather than a side effect of vaccination [personal communication]. Several studies reported on primary [25–27] and secondary [28] MMR vaccination in stable patients after solid organ transplantation (SOT). Only mild reactions were reported. Overall, studies in patients with autoimmune diseases and after SOT on low immunosuppressive therapies have shown no severe adverse events.

In some small studies, MMR vaccination was safely administered to children with leukaemia [29,30]. However, in a study published in 1962, a 2-year seronegative old boy with leukaemia on treatment with MTX (dosage not specified) was vaccinated against measles; he developed a pneumonia and died [31].

Varicella

In patients with rheumatic diseases on therapy with corticosteroids, DMARDs and/or TNFα blockers, two prospective studies were performed with a first-time varicella vaccination without safety issues [32,33]. Varicella vaccination was administered to 17 patients after kidney transplantation on therapy with prednisone, cyclosporine and azathioprine [34]. One patient developed a mild varicella rash. Several other smaller studies on varicella vaccination after SOT have been performed without any reported safety issues [26–28,35,36]. Most of the included patients had received a liver transplant; at the time of vaccination they had stable organ functions and were on low-dose immunosuppressive therapy [37].

Yellow Fever vaccination

So far, two studies have been published, in which YFV was administered to 87 patients with rheumatic diseases on therapy with DMARDs (incl. MTX) and biologicals [38,39]. No severe side effects occurred, but all vaccinations were secondary vaccinations; severe adverse events may not have emerged due to their rare frequency and the limited number of participants. In a retrospective study, 19 patients received YFV while on treatment with a variety of medications after SOT [40]. Although 17/19 vaccinations were primary YFV doses no important side effects were observed. In a cohort study, 19 patients on long-term low-dose or short-term high-dose corticosteroid treatment received a primary YFV; 15 were re-vaccinated. Apart from more local side effects, vaccination was safe [41].

Oral typhoid vaccination (OTV)

OTV (Tya21) is believed to be safe. More than 400 million doses have been administered worldwide [personal communication] and no single occurrence of a systemic infection has been reported despite the administration to HIV patients [42]. However, data in patients with immunosuppressive agents are not available and is consequently contraindicated especially due to the availability of an inactivated parenteral vaccine.

In this study we aim to add to the published scarce numbers on live vaccines in patients on immunosuppressive/immunomodulatory therapy by

- Assessing how many individuals received live vaccines while on immunosuppressive/immunodulatory therapy in three of the largest Swiss Travel Clinics over a 5-8-year time span

- Estimating the number of vaccine reactions in this group
- Comparing reactions to live vaccines among travellers on therapy with immunosuppressive/immunodulatory medications to age-and sex matched healthy travellers who received the respective vaccination at a similar time point

Rationale for study design

A retrospective design was chosen as live vaccinations are contraindicated on most immunosuppressive/immunomodulatory therapies and are only allowed after a careful risk/benefit assessment. Thus, patients that fulfil the inclusion criteria are infrequent. A retrospective and multicentre study design was consequently chosen to increase the sample size.

To overcome recall bias in the patient group we included an age-and sex matched control group of travellers without immunosuppressive/immunodulatory therapy who received the respective live vaccine in the same time period.

For some medications, it is well accepted that live vaccines may be given; one example is long-term low-dose corticosteroid therapy. However, "low-dose" is defined differently from country to country, the threshold is fore example 20mg prednisone or equivalent in the USA, Switzerland and Germany *vs.* 10mg in France and the United Kingdom [43]. In the Netherlands the decision on whether live vaccines may be given is based on the cumulative prednisone dose. MTX is another example. The thresholds have been mainly based on expert opinion and lack solid data. For this reason, we decided to include also travellers vaccinated on low-dose corticosteroid therapy and other generally accepted medications.

Methods

Study location and time frame

This retrospective study was conducted in three Travel Clinics in Switzerland: the Travel Clinic (Zentrum für Reisemedizin, ZRM) at the Epidemiology, Biostatistics and Prevention Institute, University of Zurich, the Travel Clinic of the Swiss Tropical and Public Health Institute (Swiss TPH) in Basel and the Travel Clinic at the University Hospitals of Geneva (HUG). Pre-travel data forms filled between 2010 and 2015 (ZRM and Swiss TPH, HUG: 2008-2015) were retrospectively searched for live vaccinations administered during immunosuppressive/immunomodulating therapy. Ethics approval was obtained from the Zurich, Nordwestschweiz and Geneva Ethics committees (Reference numbers KEK-ZH 2013-0188, EKNZ 257/13, CCER 2016-00218).

Data collection

Before the travel consultation, all individuals completed a form (electronic at ZRM, paper format at Swiss TPH and HUG) including demographic information, details on the planned trip and data on their medical history including taken medications. Physicians verified the information during the consultation and added information on pre-existing medical conditions, used medications and prescribed vaccinations during the current consultation.

As a first step, these forms were searched for all travellers on immunosuppressive/immunomodulatory medications (search terms in **Box 1**). In Basel and Geneva the search was performed manually. In Zurich, several collected data variables were searched electronically for the usage of an immunosuppressive/imunomodulatory medication. Amongst travellers detected by this search, those who received a live vaccine (MMR, varicella, YFV and/or OTV) were identified. Herpes Zoster vaccine was not available in Switzerland during the time period and thus could not be looked at in this study.

The identified patients were contacted by telephone and asked the questions from a pilot-tested questionnaire. If the patients could not be reached by telephone they were contacted by E-Mail. The questionnaire was developed with the input from several European vaccination and travel medicine experts during meetings of the European Network for Tropical Medicine and Travel Health (TropNet) and consecutive post-meeting electronic correspondence. The following information was gathered: visit date, age, sex, types of received vaccinations, underlying condition(s) for immunosuppressive/immunomodulatory treatment, kind of immunosuppressive/immunomodulatory medication and dosage, time between the last dose of immunosuppressant before vaccination, reactions after the vaccination in the graduation mild (not interfering in daily activities), moderate (interfering with daily activities, but able to perform daily activities) and severe (not able to perform daily activities), serious adverse reactions (death, life-threatening, persistent or significant disability or

incapacity, hospitalisation or prolongation of existing inpatient hospitalisation, congenital anomaly or birth defect, other important medical event or reaction), actions taken due to vaccine reaction.

While live vaccines are generally contraindicated under immunosuppressive therapy, "adequate" time intervals (between cessation of an immunosuppressive medication and the administration of a live vaccine) have been defined after which the administration of a live vaccine is considered safe. These time intervals differ between medications and depend on the drug's half-life and other factors. "Adequate" time interval means a sufficient interval time between drug interruption and live vaccine immunisation, while the term "critical" time interval is used when a live vaccine was given before the "adequate" time interval had elapsed. L.G. Visser's publication "The immunosuppressed Traveler" was used [44] as reference to define "adequate" time intervals. If the respective medication was not mentioned in the publication, the "adequate" time intervals as defined by the Swiss Federal Office of Public Health (FOPH) [18] were applied. In patients on corticosteroids, we differentiated between short-term (<2 weeks) and long-term (≥2weeks) use.

In the following sections of this paper the term „immunosuppressive" will include both „immunosuppressive and immunomodulatory" therapy.

In Zurich and Basel, a healthy age and sex-matched control group was enrolled. For logistical reasons, in Geneva, the inclusion of controls was not feasible. Healthy controls (HC) had to fulfil the following inclusion criteria: no immunosuppressive therapy, sex- and age-matched, same live vaccination, the live vaccination was administered at the same time point (plus/minus six months), HCs were contacted in the same way as patients. Comparative analyses were performed between immunosuppressed patients in Basel/Zurich (BS/ZH immunosuppressed) *vs.* matched HCs.

Statistical analysis

Frequencies and percentages of categorical variables were compared using Chi-squared or Fisher's exact tests as appropriate. Means, standard deviations (SD), medians and interquartile ranges (IQR) were reported and two-group comparisons were carried out using T-tests or Wilcoxon-Mann-Whitney tests as appropriate. All analyses were performed anonymously using Stata 13.1 (Stata Corp. LP, Texas, USA).

Results

Across the three travel clinics, 197 travellers on immunosuppressive therapy received a live vaccine and 116 could be interviewed for the assessment of adverse reactions (**Figure 1 - flow chart**). Sixty non-immunosuppressed controls matched to the participants from the Basel and Zurich travel clinics were interviewed.

Demographics

Contacted immunosuppressed individuals were on a mean 45.3 years (SD 15.9) old and 57 (49.1%) were male. HCs had a comparable age (46.2 years, SD 15.4) and sex distribution (n=30 (50.8%) controls were male) to Basel/Zurich travel clinic patients (average 45.7 years, SD 15.4; 31 (51.7%) male.

In the immunosuppressed patients the most common underlying diseases were rheumatic conditions (n=40, 34.5%) and inflammatory bowel diseases (n=33, 28.4%, **Table 1**).

Overall, 92 vaccinations against yellow fever, 21 against MMR, four against varicella and six OTVs were given to patients on immunosuppression. None received a sole measles vaccination (**Table 2**). Controls received 48 YFVs, 14 MMR vaccinations, four OTVs and three varicella vaccinations.

Percentages of participants who had previously received the respective administered live vaccination were comparable between immunosuppressed BS/ZH travellers and controls for YFV, mumps and rubella vaccines (data not shown). However 90.0% of controls had received a previous measles vaccinations compared to 41.7% of immunosuppressed BS/ZH patients (P=0.031).

Most common medications across all immunosuppressed participants were corticosteroids (n=45). In all immunosuppressed travellers, the prednisone equivalent dosage was 7.5mg/day on a median, IQR 5-20mg/day; for long-term (>2 weeks) use: 7.5mg/day, range: 1.25mg-80mg/day; and for short-term use (<2 weeks): 45mg a day, range: 5mg-840mg a day. Four patients (2 patients with 20mg/day, one 50mg/day and one with 80mg/day) with long-term therapy were above the "permitted" maximum of ≥20mg/day prednisone dose per day according to the Swiss vaccination recommendations [18].

The second most frequent drug was mesalazine (n=28), followed by MTX (n=19, weekly dose: median 12.5mg, IQR 10-20mg), with two patients treated with weekly MTX-dosages above 20mg, one with 22.5mg and one with 100mg. In the patient with a weekly dosage of 100mg, the last MTX-intake was 4 days before re-vaccination against yellow fever. The other patient had received YFV outside the "critical" time interval.

Live vaccines were also given on biological therapies, such as TNF-alpha inhibitors (n=8 travellers, **Table 2**).

All but five patients were on current immunosuppressive therapy (or in "critical time interval" after cessation/pausing of an immunosuppressive medication). In five travellers, adequate time intervals had elapsed since the last treatment dose was taken: One patient who received an MMR vaccine had taken the last MTX dose of 20mg 42 days before vaccination, two other individuals on MTX (20-25mg and 5mg/week) received the YFV 91 and 106 days after the last dose was taken, another patient on ustekinumab received a YFV 143 days after the last dose; and one patient on 75mg 6-mercaptopurine therapy took the last dose 135 days before YFV.

In BS/ZH immunosuppressed, on average, 0.6 (SD 0.7) inactivated vaccines were given at the time of live vaccine administration. In HCs, on average 0.9 (SD 1.0) inactivated vaccines were simultaneously administered (P=0.14).

Safety assessment

Overall, 22/116 (19.0%) of patients on immunosuppressive therapy reported reactions after the vaccination (**Figure 2**).

Nine (7.8%) remembered local reactions, such as muscle pain or tension. Seven reactions were rated as mild; one patient with multiple sclerosis on interferon beta treatment reported a severe local reaction after a primary MMR vaccination.

14/116 (12.2%) patients had systemic reactions: six (5.2%) had mild muscle and joint pain, four (3.5%) had flu-like symptoms, one of them with painful lymph nodes and nausea; two (1.7%) remembered fatigue, and one reported (0.9%) fever. Out of the systemic reactions, 11 were mild, two were moderate and one person with rheumatoid arthritis on treatment with sulfasalazine remembered severe muscle/joint pain after a primary YFV.

Among HCs, 15/60 (25.0%) remembered reactions after the vaccination. 7/60 (11.7%) reported local reactions, such as muscle pain, haematoma or sensitive puncture. All local reactions were mild. 8/60 (13.3%) HCs reported systemic side reactions; three (5.0%) remembered fatigue, one of them with fever. Two had (3.3%) flu-like symptoms and 4 (6.7%) had muscle/joint pain after the vaccination. Five systemic reactions were categorised as mild and two as moderate.

There was no significant difference in percentages of local reactions and systemic reactions between controls and BS/ZH immunosuppressed (both P values=1.0).

Likewise, severity of local and systemic reactions was comparable between the immunosuppressed and HCs. However, none of the HCs reported a severe reaction.

No serious adverse event was reported.

In the five patients with “adequate time” intervals between cessation of immunosuppressive treatment and live vaccination, only one noticed mild muscle/joint pain. None of the five patients vaccinated in the “critical” time interval receiving long-term (≥2weeks) high-dose-corticosteroid treatment (≥20mg/day prednisone equivalent/day) or high-dose-MTX had side effects.

Discussion

We conducted a retrospective study in immunosuppressed travellers who received a live vaccination in three Swiss Travel Centres. We identified 197 patients on immunosuppression who were vaccinated against YF, MMR, varicella or typhoid and 116 could be interviewed for assessment of experienced side effects. No serious reaction was reported. Local and systemic reactions occurred as frequently in a matched HC group (25.0%) as in the immunosuppressed (19.0%).

Serious reactions due to live vaccines are extremely rare. It is estimated that a YEL-AVD (yellow fever vaccine-associated viscerotropic disease) occurs in 0.4 of 100.000 administered vaccine doses, with 1.0 per 100.000 doses in the >60-year olds and 2.3 per 100.000 administered doses in individuals aged ≥70 [45]. Thus our sample was too small to detect a severe case, particularly on a specific immunosuppressive regimen and vaccine, as immunosuppressive regimens were diverse.

Moreover, according to the Swiss vaccination recommendations in patients with rheumatic diseases live vaccines are allowed on long-term (≥2weeks) low-dose corticosteroid (<20mg/day prednisone) non-systemic corticosteroid therapy, and methotrexate ≤20mg/week [18]. Short-term (<2 weeks) high-dose-corticosteroid treatment (≥20mg/day prednisone equivalent/day) is usually permitted but some some experts will still wait two weeks or more before administering live vaccines [46]. As previously stated, because recommendations have been mainly based on expert opinion and lack solid data, we decided to include also travellers vaccinated on low-dose corticosteroid therapy and other generally accepted medications. 65.5% of all patients observed in our study might be considered to be on a weak immunosuppressive regimen (including budesonid, glatiramer acetate, interferon, mesalazine, sulfasalazine, long-term low-dose corticosteroid and short-term high-dose-corticosteroid treatment). No difference between high or weak immunosuppressive regimen was observed with regard to percentages of side effects, local reactions, systemic reactions and severity [data not shown].

Another limitation is the rapidly increasing diversity of immunosuppressive therapies, with the consequence that our study cannot be generalised to new medications. However, as severe reactions after live vaccinations may occur more often in the immunocompromised, the paucity of data on this topic makes us believe that even small sample size studies are important to be known by practitioners in travel medicine.

Due to the retrospective study design, live vaccines were administered between 14 days and five years prior to the conducted interviews. Thus reduced recall on experienced vaccine reactions may have limited the obtained results. However, we believe that severe and serious reactions would have been recalled even after a five-year time span. We additionally tried to limit recall bias by contacting age- and sex-matched HCs who had received the same vaccine during a similar time period. However, we cannot exclude that recall may differ in those with a pre-existing condition as they might have been more alert of vaccine reactions than healthy individuals.

Furthermore, it is possible that some vaccinees had very serious reactions, which may even have led to death, and thus could not be reached for an interview. Nevertheless, the safety division of Swissmedic has not detected a severe infection with a vaccine strain in an immunosuppressed patient between 2001 and May 2016 [personal communication].

On the other hand, the study can give some cautious data on effectiveness. No yellow fever case was reported in the Swiss population during the relevant time span, so we can be rather sure that none of the vaccinees was diagnosed with yellow fever. However, among measles cases reported in Switzerland, we do not know how many occurred in (vaccinated) immunosuppressed persons.

Conclusion

The decision on whether live vaccines can be given to immunosuppressed patients is a daily encountered challenge by specialists of varying backgrounds. In immunosuppressed patients, live-attenuated vaccines can potentially be harmful if the vaccine strain reverts to the original pathogen and infects the vaccinated person. On the other hand these patients profit especially from these vaccinations as they are particularly vulnerable to vaccine-preventable infections [47–49]. Apart from infecting the immunosuppressed person, other vaccine-related local or systemic reactions are feared as well as re-activation of the underlying disease.

By making our data on live vaccinations in immunosuppressed patients available to a wide audience our aim is to contribute to the currently scarce literature on this topic. From these additional data it is impossible to conclude that live vaccines can be safely given to immunosuppressed patients. However, despite the limitations discussed above it is re-assuring that in the examined patient groups serious side effects or infections by the attenuated vaccine strain did not occur.

Acknowledgements

We would like to thank all experts from the TropNet network for their input during the questionnaire development and we thank the staff in all three travel centres for providing advice to immunosuppressed travellers. We also thank Valeriu Toma from Swissmedic (the Swiss Agency for Therapeutic Products) for sharing with us information on vaccine reactions in immunosuppressed patients.

Conflicts of interest

None

Author Contribution

All authors have made substantial contributions to either of the following: the design of the study, analysis and interpretation of data, drafting the article or revising it critically for important intellectual content. All authors have approved the final version of the manuscript.

References

[1] Baaten GG, Geskus RB, Kint JA, Roukens AH, Sonder GJ, van den Hoek A. Symptoms of infectious diseases in immunocompromised travelers: a prospective study with matched controls. J Travel Med 2011;18:318–26.

[2] Jaeger VK, Rüegg R, Steffen R, Hatz C, Bühler S. Travelers with immune-mediated inflammatory diseases: are they different? J Travel Med 22:161–7.

[3] Mikati T, Taur Y, Seo SK, Shah MK. International travel patterns and travel risks of patients diagnosed with cancer. J Travel Med n.d.;20:71–7.

[4] Bialy C, Horne K, Dendle C, Kanellis J, Littlejohn G, Ratnam I, et al. International travel in the immunocompromised patient: a cross-sectional survey of travel advice in 254 consecutive patients. Intern Med J 2015;45:618–23.

[5] Wieten RW, Leenstra T, Goorhuis A, Van Vugt M, Grobusch MP. Health risks of travelers with medical conditions-a retrospective analysis. J Travel Med 2012;19:104–10.

[6] Rahier J-F. Management of IBD Patients with Current Immunosuppressive Therapy and Concurrent Infections. Dig Dis 2015;33 Suppl 1:50–6.

[7] Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum 2002;46:2287–93.

[8] Singh J, Wells G, Christensen R, Tanjong Ghogomu E, Maxwell L, Jk M, et al. Adverse effects of biologics : a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev 2011:CD008794.

[9] Dekkiche S, de Vallière S, D'Acremont V, Genton B. Travel-related health risks in moderately and severely immunocompromised patients: a case-control study. J Travel Med 2016;23:taw001.

[10] Kengsakul K, Sathirapongsasuti K, Punyagupta S. Fatal myeloencephalitis following yellow fever vaccination in a case with HIV infection. J Med Assoc Thai 2002;85:131–4.

[11] Schrauder A, Henke-Gendo C, Seidemann K, Sasse M, Cario G, Moericke A, et al. Varicella vaccination in a child with acute lymphoblastic leukaemia. Lancet 2007;369:1232.

[12] Centers for Disease Control and Prevention. Measles Pneumonitis Following Measles-Mumps-Rubella Vaccination of a Patient with HIV Infection, 1993 1996.

[13] Centers for Disease Control and Prevention. Immunocompromised Travelers - Chapter 8 - 2014 Yellow Book | Travelers' Health | CDC 2014.

[14] van Assen S, Agmon-Levin N, Elkayam O, Cervera R, Doran MF, Dougados M, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2011;70:414–22.

[15] Papadopoulou D, Sipsas N V. Comparison of national clinical practice guidelines and recommendations on vaccination of adult patients with autoimmune rheumatic diseases. Rheumatol Int 2013.

[16] Repo H, Peltomaa R, Finnish Rheumatology Association. Vaccination of adults with inflammatory rheumatic diseases. 2012.

[17] Eperon G, Vaudaux B. Vaccination chez le voyageur immunosupprimé. Rev Med Suisse; 9970-8 2013:970–8.

[18] Bundesamt für Gesundheit (BAG), Eidenössische Kommission für Impffragen (EKIF). Impfprinzipien und Empfehlungen für Personen mit autoimmunentzündlichen rheumatischen Erkrankungen 2014:159–61.

[19] Office fédéral de la santé publique (OFSP) C fédérale pour les vaccinations (CFV). Vaccination des personnes avec maladies rhumatismales auto-immunes inflammatoires : résumé des principes et recommandations. 2014.

[20] Bühler S, Eperon G, Ribi C, Kyburz D, van Gompel F, Visser LG, et al. Vaccination recommendations for adult patients with autoimmune inflammatory rheumatic diseases. Swiss Med Wkly 2015;145:w14159.

[21] Borte S, Liebert UG, Borte M, Sack U. Efficacy of measles, mumps and rubella revaccination in children with juvenile idiopathic arthritis treated with methotrexate and etanercept. Rheumatology (Oxford) 2009;48:144–8.

[22] Heijstek MW, Pileggi GCS, Zonneveld-Huijssoon E, Armbrust W, Hoppenreijs EPAH,

Uiterwaal CSPM, et al. Safety of measles, mumps and rubella vaccination in juvenile idiopathic arthritis. Ann Rheum Dis 2007;66:1384–7.
[23] Heijstek MW, Gorter S, Vries LD De, Smits GP, Gageldonk PG Van, Berbers GAM, et al. Effects of the Live Attenuated Measles-Mumps-Rubella Booster Vaccination With Juvenile Idiopathic Arthritis. JAMA 2013;309.
[24] Pileggi GS, Terreri MTRA, Barbosa CP, Ferriani, V.P.L. Measles, mumps and rubella vaccination safety in patients with juvenile rheumatic diseases taking immunosuppressive drugs. Ann Rheum Dis 2013;71, 2013.
[25] Rand EB, McCarthy CA, Whitington PF. Measles vaccination after orthotopic liver transplantation. J Pediatr 1993;123:87–9.
[26] Shinjoh M, Hoshino K, Takahashi T, Nakayama T. Updated data on effective and safe immunizations with live-attenuated vaccines for children after living donor liver transplantation. Vaccine 2015;33:701–7.
[27] Khan S, Erlichman J, Rand EB. Live virus immunization after orthotopic liver transplantation. Pediatr Transplant 2006;10:78–82.
[28] Kano H, Mizuta K, Sakakihara Y, Kato H, Miki Y, Shibuya N, et al. Efficacy and safety of immunization for pre- and post- liver transplant children. Transplantation 2002;74:543–50.
[29] Nilsson a., De Milito A, Engstrom P, Nordin M, Narita M, Grillner L, et al. Current Chemotherapy Protocols for Childhood Acute Lymphoblastic Leukemia Induce Loss of Humoral Immunity to Viral Vaccination Antigens. Pediatrics 2002;109:e91–e91.
[30] S. T, Hirai S, Oitani K, Ito M, Ihara T, Iwasa T, et al. Application of Live attenuated measles and mumps vaccines in children with acute leukemia. Biken J 1981;24:147–51.
[31] Mitus A, Holloway A, Evans AE, Enders JF. Attenuated measles vaccine in children with acute leukemia. Am J Dis Child 1962;103.
[32] Pileggi GS, de Souza CBS, Ferriani VPL. Safety and immunogenicity of varicella vaccine in patients with juvenile rheumatic diseases receiving methotrexate and corticosteroids. Arthritis Care Res (Hoboken) 2010;62:1034–9.
[33] Pileggi GS, de Souza CBS, Ferriani VPL. Safety and efficacy of varicella vaccine in patients with juvenile rheumatic diseases: A five years experience. Ann Rheum Dis 2012;71(Suppl3)430, 2012.
[34] Zamora I, Simon JM, Da Silva ME, Piqueras AI. Attenuated varicella virus vaccine in children with renal transplants. Pediatr Nephrol 1994;8:190–2.
[35] Weinberg A, Horslen SP, Kaufman SS, Jesser R, Devoll-Zabrocki A, Fleckten BL, et al. Safety and immunogenicity of varicella-zoster virus vaccine in pediatric liver and intestine transplant recipients. Am J Transplant 2006;6:565–8.
[36] Posfay-Barbe KM, Pittet LF, Sottas C, Grillet S, Wildhaber BE, Rodriguez M, et al. Varicella-zoster immunization in pediatric liver transplant recipients: safe and immunogenic. Am J Transplant 2012;12:2974–85.
[37] Croce E, Hatz C, Jonker EF, Visser LG, Jaeger VK, Bühler S. Safety of live vaccinations on immunosuppressive therapy in patients with immune-mediated inflammatory diseases, solid organ transplantation or after bone-marrow transplantation - A systematic review of randomized trials, observational studies and case reports. Vaccine 2017;35:1216–26.
[38] Mota LM, Oliveira AC, Lima RA, Santos-Neto LL, Tauil PL. [Vaccination against yellow fever among patients on immunosuppressors with diagnoses of rheumatic diseases]. Rev Soc Bras Med Trop 2009;42:23–7.
[39] Scheinberg M, Guedes-Barbosa LS, Mangueira C, Rosseto EA, Mota L, Oliveira AC, et al. Yellow fever revaccination during infliximab therapy. Arthritis Care Res 2010;62:896–8.
[40] Azevedo LS, Lasmar EP, Contieri FLC, Boin I, Percegona L, Saber LTS, et al. Yellow fever vaccination in organ transplanted patients: is it safe? A multicenter study. Transpl Infect Dis 2012;14:237–41.
[41] Kernéis S, Launay O, Ancelle T, Iordache L, Naneix-Laroche V, Méchaï F, et al. Safety and immunogenicity of yellow fever 17D vaccine in adults receiving systemic corticosteroid therapy: An observational cohort study. Arthritis Care Res (Hoboken) 2013.
[42] Banda R, Yambayamba V, Lalusha BD, Sinkala E, Kapulu MC, Kelly P. Safety of live, attenuated oral vaccines in HIV-infected Zambian adults: oral vaccines in HIV. Vaccine 2012;30:5656–60.

[43] Papadopoulou D, Sipsas N V. Comparison of national clinical practice guidelines and recommendations on vaccination of adult patients with autoimmune rheumatic diseases. Rheumatol Int 2014;34:151–63.
[44] Visser LG. The immunosuppressed traveler. Infect Dis Clin North Am 2012;26:609–24.
[45] Centers for Disease Control and Prevention. Notes from the Field: Fatal Yellow Fever Vaccine–Associated Viscerotropic Disease — Oregon, September 2014. Morb Mortal Wkly Rep 2015:March 20, 2015 / 64(10);279–81.
[46] The Centers for Disease Control and Prevention. Yellow Book. Chapter 8 Advising Travelers with Specific Needs. Immunocompromised Travelers 2018.
[47] Blumentals WA, Arreglado A, Napalkov P, Toovey S. Rheumatoid arthritis and the incidence of influenza and influenza-related complications: a retrospective cohort study. BMC Musculoskelet Disord 2012;13:158.
[48] Wotton CJ, Goldacre MJ. Risk of invasive pneumococcal disease in people admitted to hospital with selected immune-mediated diseases: record linkage cohort analyses. J Epidemiol Community Health 2012;66:1177–81.
[49] Vonkeman H, ten Napel C, Rasker H, van de Laar M. Disseminated primary varicella infection during infliximab treatment. J Rheumatol 2004;31:2517–8.